Sequestration of Vascular Endothelial Growth Factor (VEGF) Induces Late Restrictive Lung Disease.

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Public Summary:
Neonatal respiratory distress syndrome is a restrictive lung disease characterized by surfactant deficiency. Decreased vascular endothelial growth factor (VEGF), which demonstrates important roles in angiogenesis and vasculogenesis, has been implicated in the pathogenesis of restrictive lung diseases. Current animal models investigating VEGF in the etiology and outcomes of RDS require premature delivery, hypoxia, anatomically or temporally limited inhibition, or other supplemental interventions. Consequently, little is known about the isolated effects of chronic VEGF inhibition, started at birth, on subsequent developing lung structure and function. OBJECTIVES: To determine whether inducible, mesenchyme-specific VEGF inhibition in the neonatal mouse lung results in long-term modulation of AECII and whole lung function. METHODS: Triple transgenic mice expressing the soluble VEGF receptor sFlt-1 specifically in the mesenchyme (Dermo-1/rtTA/sFlt-1) were generated and compared to littermate controls at 3 months to determine the impact of neonatal downregulation of mesenchymal VEGF expression on lung structure, cell composition and function. Reduced tissue VEGF bioavailability has previously been demonstrated with this model. MEASUREMENTS AND MAIN RESULTS: Triple transgenic mice demonstrated restrictive lung pathology. No differences in gross vascular development or protein levels of vascular endothelial markers was noted, but there was a significant decrease in perivascular smooth muscle and type I collagen. Mutants had decreased expression levels of surfactant protein C and hypoxia inducible factor 1-alpha without a difference in number of type II pneumocytes. CONCLUSIONS: These data show that mesenchyme-specific inhibition of VEGF in neonatal mice results in late restrictive disease, making this transgenic mouse a novel model for future investigations on the consequences of neonatal RDS and potential interventions.

Scientific Abstract:
RATIONALE: Neonatal respiratory distress syndrome is a restrictive lung disease characterized by surfactant deficiency. Decreased vascular endothelial growth factor (VEGF), which demonstrates important roles in angiogenesis and vasculogenesis, has been implicated in the pathogenesis of restrictive lung diseases. Current animal models investigating VEGF in the etiology and outcomes of RDS require premature delivery, hypoxia, anatomically or temporally limited inhibition, or other supplemental interventions. Consequently, little is known about the isolated effects of chronic VEGF inhibition, started at birth, on subsequent developing lung structure and function. OBJECTIVES: To determine whether inducible, mesenchyme-specific VEGF inhibition in the neonatal mouse lung results in long-term modulation of AECII and whole lung function. METHODS: Triple transgenic mice expressing the soluble VEGF receptor sFlt-1 specifically in the mesenchyme (Dermo-1/rtTA/sFlt-1) were generated and compared to littermate controls at 3 months to determine the impact of neonatal downregulation of mesenchymal VEGF expression on lung structure, cell composition and function. Reduced tissue VEGF bioavailability has previously been demonstrated with this model. MEASUREMENTS AND MAIN RESULTS: Triple transgenic mice demonstrated restrictive lung pathology. No differences in gross vascular development or protein levels of vascular endothelial markers was noted, but there was a significant decrease in perivascular smooth muscle and type I collagen. Mutants had decreased expression levels of surfactant protein C and hypoxia inducible factor 1-alpha without a difference in number of type II pneumocytes. CONCLUSIONS: These data show that mesenchyme-specific inhibition of VEGF in neonatal mice results in late restrictive disease, making this transgenic mouse a novel model for future investigations on the consequences of neonatal RDS and potential interventions.